Results of an Initial Phase II Study using an Oncolytic Herpes Simplex Virus, NV1020, Administered Repeatedly via Hepatic Artery Infusion Prior to 2nd Line Chemotherapy, in Patients with Colorectal Adenocarcinoma Metastatic to the Liver

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Treatment Rationale

- Oncolytic viruses have potential as effective new anticancer agents.[1,2]
- NV1020 is a modified, replication-competent Herpes simplex virus with marked antitumor activity in animal models.[3] Additive effects have been reported in combination with conventional chemotherapy.
- An initial Phase 1 study using single intrahepatic artery infusions of NV1020 reported NV1020 to be well tolerated in patients with mCRC; transient hepatic enzyme and prothrombin time increases with single doses of $1X10^8$ pfu were considered dose-limiting.[4,5] This study also described encouraging tumor responses after 2nd-line chemotherapy, thus prompting initiation of a follow-up, Phase 1/2 study using multiple doses of NV1020.
- Safety results from the dose-ranging (Phase 1) part of the latter study have been published, except for transient (<24 hr) viral syndrome, no significant related toxicity was found and an optimal biological dose (OBD) was selected for early Phase 2 evaluation.[6]
- Safety and efficacy outcomes using the OBD are now presented, with follow up exceeding 12 months in all patients.

Methods (Figure 1)

- Open-label, dose-ranging study design (Phase 1, n=3 / dose cohort), followed by expansion of one 'optimal biological dose' cohort (Phase 2)
- Patients (HSV-1 seropositive) had failed standard chemotherapy (up to 5 agents; all FDA-approved for CRC) and showed tumor progression, with liver-dominant metastases on ^{18}F FDG PET/CT scans.
- Four weekly NV1020 infusions were administered via transfemoral catheter into the hepatic artery (dose cohorts of $3x10^6$, $1x10^7$, $3x10^7$, $1 x10^8$ pfu). Highest dose was selected as OBD for cohort expansion and evaluation in Phase 2.
- NV1020 was followed by a minimum two cycles of additional conventional chemotherapy
- Safety was monitored clinically and with laboratory tests, using NCI-CTC for dose-limiting toxicity (DLT). Data were reviewed periodically by an independent Data Safety Monitoring Board.
- Efficacy was determined by blinded, independent radiology panel, using modified RECIST for CT images and EORTC criteria (based on SUV_{max}) for PET
- Follow-up was every 3 months for one year (safety and tumor response) and then by telephone for life (for late-onset adverse events and overall survival).

Phase 2 Results

Patient Characteristics:

- 22 patients evaluable for safety and efficacy using the OBD
  - 73% male; mean 57 yrs old, 95% ≥90 KPS
  - Median 95 weeks (range 26-223) since primary colorectal cancer resection
  - 55% had pulmonary metastases in addition to their liver-dominant mCRC
  - Mean CEA was 187 ng/mL (range: 2-1560)
- 100% had prior 5FU-based chemotherapy; 77% and 58% had oxaliplatin and irinotecan respectively (50% both agents), 86% had one targeted therapy (24% ≥2 such agents), 29% had radiofrequency ablation.
- 18 (82%) patients completed full treatment as scheduled; only 2 (9%) discontinued NV1020 prematurely (after 2 infusions) due to tumor progression and rapidly fatal clinical decline. Two (9%) refused both cycles of post NV1020 chemotherapy due to personal reasons.
- Post NV1020 chemotherapy comprised only drugs to which 45% patients were previously refractory to. Only one new agent was administered to 36% patients

Clinical Safety:

- Post infusion febrile reaction was the most common adverse event (95% patients)
  - Maximum 104°F (Grade 2), duration 6 – 24 hours
  - Associated with rigors (55%), myalgia (56%), headache (41%) and fatigue (32%)
  - Effectively managed with antipyretics and analgesia
- Other common, NV1020-related, Grade 1/2 events were nausea (45%), vomiting (27%)
- Grade 3 toxicity: lymphopenia in two patients (10%) (occurrence after initial infusion of NV1020; asymptomatic; transient (<7 days); not treated, subsequent infusions were associated with Grade 1 lymphopenia)
- No NV1020-related serious adverse events were reported at any time

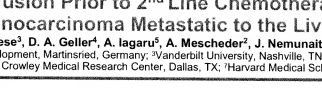

Figure 1. Study Design

Figure 2. CT and FDG PET changes after NV1020 alone and after 2 cycles of chemotherapy

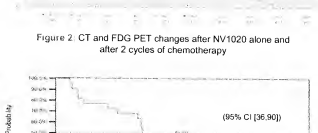

Figure 3: Survival Probability (Kaplan Meier) (N=22)

Results (continued)

Laboratory Findings:

- Increases in all measured cytokines (IL-6, TNFα, IFNγ)
  - Peaks = 8 hrs, all returning to baseline by 24 hrs
- Asymptomatic perturbations in D-dimers, prothrombin time, platelets, lymphocyte, neutrophil counts, C-Reactive protein
- No NV1020-related changes in liver function.

Viral Activity:

- NV1020 neutralizing antibodies rose in all patients but no NV1020 shedding was detected (PCR analysis of serial samples of serum, saliva or skin [genitalia] swabs up to 14 days post infusion)
- Intermittent shedding of wild-type HSV-1 was found in 55% patients (comparable rate to historical controls)
- 68% patients HSV-2 seronegative at baseline became seropositive post NV1020 (NV1020 contains a 5.2kb fragment of HSV-2 DNA [incl. HSV-2 glycoprotein G])

Other safety outcomes:

- No consistent, virus-related trends or abnormalities were identified for full physical examinations (emphasis on neurological testing and skin/mucosa), ECGs and 'mini-mental' tests

Efficacy (Figures 2 & 3):

After NV1020 alone:

- 10/22 (45%) Stable Disease on CT, 8/20 (40%) Stable Disease on PET

Best response after chemotherapy

- 12/22 (55%) clinical response on CT (1CR, 1PR, 10SD)
- 13/22 (59%) clinical response on PET (5PR, 8SD)
- Despite intrahepatic delivery of NV1020, some remote responses were observed
- Response showed no correlation with initial tumor size, SUV or CEA, nor with time since primary resection, nor with pre- or post NV1020 chemotherapy type
- Kaplan-Meier median time to progression = 28 weeks (95% CI [9,37])
- Kaplan-Meier median survival = 52 weeks (95% CI [36,90])
- Nine (41%) patients remain alive > 1 year after NV1020 administration

Conclusions

1. Repeated intrahepatic infusions of $1x10^8$ pfu NV1020 are remarkably well tolerated
   i) Cytokine-mediated viral reaction is transient, mild and easily managed with antipyretics/analgesia
   ii) Consistent, asymptomatic, immunological effects (neutralizing antibody, HSV-2 seroconversion) were observed
   iii) Virus delivery was well documented by investigators and patients.
2. No adverse interactions were reported with follow-up chemotherapeutic agents.
3. NV1020 stabilizes liver metastases in highly advanced, refractory mCRC and may sensitize tumors to salvage chemotherapy and extend survival.
4. A controlled Phase 2/3 controlled clinical trial is now justified.

References:

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EXHIBIT E